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(54) Title: POLYNUCLEOTIDES ENCODING NOVEL SECRETED PROTEINS

(57) Abstract: Isolated polynucleotides which have been derived from a variety of human tissue sources, and which encode novel secreted proteins, are provided. Also provided are methods for producing proteins using these polynucleotides, and the proteins so produced.

POLYNUCLEOTIDES ENCODING NOVEL SECRETED PROTEINS

RELATED APPLICATIONS

This application claims the benefit of prior-filed provisional patent application U.S. Serial No. 60/194,941 entitled "Polynucleotides Encoding Novel Secreted Proteins", filed April 6, 2000. The content of the above-referenced application is incorporated in its entirety.

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Gargantuan efforts have been employed by various investigational projects to randomly sequence portions of naturally-occurring cDNAs. The rationale behind this approach to identification and sequencing genes is founded in two basic principles: (1) that transcribed cDNAs represent the product of the most important genes, namely those that are actually expressed *in vivo*, and (2) that efforts to sequence genes and other portions of the genome of target organisms which are not actually expressed wastes substantial effort on areas not likely to yield genetic information of therapeutic importance. Thus, the high-throughput sequencing efforts focus on only those portions of the genome which are expressed. The randomly produced cDNA sequences represent "expressed sequence tags" or "ESTs", which identify and can be used as probes for the longer, full-length cDNA or genomic sequence from which they were transcribed.

Although this "shortcut" approach to genomic sequencing presents savings of effort compared to sequencing of the complete genome, it still produced a vast array of ESTs which may not be directly useful as protein therapeutics. To date, the majority of protein-related drug discovery has focused on the use of secreted proteins to produce a desired therapeutic effect. Since the EST approach theoretically identifies all expressed proteins, it produces an EST library which contains a mixture of secreted proteins (such as hormones, cytokines and receptors) and non-secreted proteins (such as, for example, metabolic enzymes and cellular structural proteins), without identifying which ESTs correspond to proteins falling into either category. As a result, these methods are not optimally tailored to the needs of investigators searching for secreted proteins because they must separate the secreted "wheat" from the non-secreted "chaff", wasting effort and resources in the process.

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning).

More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. Co-assigned U.S. Patent No. 5,536,637, which is incorporated herein by reference, provides methods for focusing genomic sequencing efforts on sequences encoding the secreted proteins which are of most interest for identification of protein therapeutics. The '637 patent discloses a "signal sequence trap" which selectively identifies partial sequences encoding secreted proteins, namely "secreted expressed sequence tags" or "sESTs". The sequences of these sESTs can be used to design probes to isolate the full-length cDNA clones that encode secreted proteins.

It is to these secreted proteins and the full-length polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

The present invention provides for full-length cDNAs isolated from a variety of human RNA/cDNA sources which encode novel secreted proteins.

In preferred embodiments, the present invention provides an isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID

NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID

NO:242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO:245, SEQ ID NO:246, SEQ ID NO:247, SEQ ID NO:248, SEQ ID NO:249, SEQ ID NO:250, SEQ ID NO:251, SEQ ID NO:252, SEQ ID NO:253, SEQ ID NO:254, SEQ ID NO:255, SEQ ID NO:256, SEQ ID NO:257, SEQ ID NO:258, SEQ ID NO:259, SEQ ID NO:260, SEQ ID NO:261, SEQ ID NO:262, SEQ ID NO:263, SEQ ID NO:264, SEQ ID NO:265, SEQ ID NO:266, SEQ ID NO:267, SEQ ID NO:268, SEQ ID NO:269, SEQ ID NO:270, SEQ ID NO:271, SEQ ID NO:272, SEQ ID NO:273, SEQ ID NO:274, SEQ ID NO:275, SEQ ID NO:276, SEQ ID NO:277, SEQ ID NO:278, SEQ ID NO:279, SEQ ID NO:280, SEQ ID NO:281, SEQ ID NO:282, SEQ ID NO:283, SEQ ID NO:284, SEQ ID NO:285, SEQ ID NO:286, SEQ ID NO:287, SEQ ID NO:288, SEQ ID NO:289, SEQ ID NO:290, SEQ ID NO:291, SEQ ID NO:292, SEQ ID NO:293, SEQ ID NO:294, SEQ ID NO:295, SEQ ID NO:296, SEQ ID NO:297, SEQ ID NO:298, SEQ ID NO:299, SEQ ID NO:300, SEQ ID NO:301, SEQ ID NO:302, SEQ ID NO:303, SEQ ID NO:304, SEQ ID NO:305, SEQ ID NO:306, SEQ ID NO:307, SEQ ID NO:308, SEQ ID NO:309, SEQ ID NO:310, SEQ ID NO:311, SEQ ID NO:312, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:315, SEQ ID NO:316, SEQ ID NO:317, SEQ ID NO:318, SEQ ID NO:319, SEQ ID NO:320, SEQ ID NO:321, SEQ ID NO:322, SEQ ID NO:323, SEQ ID NO:324, SEQ ID NO:325, SEQ ID NO:326, SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:329, SEQ ID NO:330, SEQ ID NO:331, SEQ ID NO:332, SEQ ID NO:333, SEQ ID NO:334, SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO:338, SEQ ID NO:339, SEQ ID NO:340, SEQ ID NO:341, SEQ ID NO:342, SEQ ID NO:343, SEQ ID NO:344, SEQ ID NO:345, SEQ ID NO:346, SEQ ID NO:347, SEQ ID NO:348, SEQ ID NO:349, SEQ ID NO:350, SEQ ID NO:351, SEQ ID NO:352, SEQ ID NO:353, SEQ ID NO:354, SEQ ID NO:355, SEQ ID NO:356, SEQ ID NO:357, SEQ ID NO:358, SEQ ID NO:359, SEQ ID NO:360, SEQ ID NO:361, SEQ ID NO:362, SEQ ID NO:363, SEQ ID NO:364, SEQ ID NO:365, SEQ ID NO:366, SEQ ID NO:367, SEQ ID NO:368, SEQ ID NO:369, SEQ ID NO:370, SEQ ID NO:371, SEQ ID NO:372, SEQ ID NO:373, SEQ ID NO:374, SEQ ID NO:375, SEQ ID NO:376, SEQ ID NO:377, SEQ ID NO:378, SEQ ID NO:379, SEQ ID NO:380, SEQ ID NO:381, SEQ ID NO:382, SEQ ID NO:383, SEQ ID NO:384, SEQ ID NO:385, SEQ ID NO:386, SEQ ID NO:387, SEQ ID NO:388, SEQ ID NO:389, SEQ ID NO:390, SEQ ID NO:391, SEQ ID NO:392, SEQ ID NO:393, SEQ ID NO:394, SEQ ID NO:395, SEQ ID NO:396, SEQ ID NO:397, SEQ ID NO:398, SEQ ID NO:399, SEQ ID NO:400, SEQ ID NO:401, SEQ ID NO:402, SEQ ID NO:403, SEQ ID NO:404, SEQ ID NO:405, SEQ ID NO:406, SEQ ID NO:407, SEQ ID NO:408, SEQ ID NO:409, SEQ ID NO:410, SEQ ID NO:411, SEQ ID NO:412, SEQ ID NO:413, SEQ ID NO:414, SEQ ID NO:415, SEQ ID NO:416, SEQ ID NO:417, SEQ ID NO:418, SEQ ID NO:419, SEQ ID NO:420, SEQ ID NO:421, SEQ ID NO:422, SEQ ID NO:423, SEQ ID NO:424, SEQ ID NO:425, SEQ ID NO:426, SEQ ID

NO:427, SEQ ID NO:428, SEQ ID NO:429, SEQ ID NO:430, SEQ ID NO:431, SEQ ID NO:432, SEQ ID NO:433, SEQ ID NO:434, SEQ ID NO:435, SEQ ID NO:436, SEQ ID NO:437, SEQ ID NO:438, SEQ ID NO:439, SEQ ID NO:440, SEQ ID NO:441, SEQ ID NO:442, SEQ ID NO:443, SEQ ID NO:444, SEQ ID NO:445, SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:449, SEQ ID NO:450, SEQ ID NO:451, SEQ ID NO:452, SEQ ID NO:453, SEQ ID NO:454, SEQ ID NO:455, SEQ ID NO:456, SEQ ID NO:457, SEQ ID NO:458, SEQ ID NO:459, SEQ ID NO:460, SEQ ID NO:461, SEQ ID NO:462, SEQ ID NO:463, SEQ ID NO:464, SEQ ID NO:465, SEQ ID NO:466, SEQ ID NO:467, SEQ ID NO:468, SEQ ID NO:469, SEQ ID NO:470, SEQ ID NO:471, SEQ ID NO:472, SEQ ID NO:473, SEQ ID NO:474, SEQ ID NO:475, SEQ ID NO:476, SEQ ID NO:477, SEQ ID NO:478, SEQ ID NO:479, SEQ ID NO:480, SEQ ID NO:481, SEQ ID NO:482, SEQ ID NO:483, SEQ ID NO:484, SEQ ID NO:485, SEQ ID NO:486, SEQ ID NO:487, SEQ ID NO:488, SEQ ID NO:489, SEQ ID NO:490, SEQ ID NO:491, SEQ ID NO:492, SEQ ID NO:493, SEQ ID NO:494, SEQ ID NO:495, SEQ ID NO:496, SEQ ID NO:497, SEQ ID NO:498, SEQ ID NO:499, SEQ ID NO:500, SEQ ID NO:501, SEQ ID NO:502, SEQ ID NO:503, SEQ ID NO:504, SEQ ID NO:505, SEQ ID NO:506, SEQ ID NO:507, SEQ ID NO:508, SEQ ID NO:509, SEQ ID NO:510, SEQ ID NO:511, SEQ ID NO:512, SEQ ID NO:513, SEQ ID NO:514, SEQ ID NO:515, SEQ ID NO:516, SEQ ID NO:517, SEQ ID NO:518, SEQ ID NO:519, SEQ ID NO:520, SEQ ID NO:521, SEQ ID NO:522, SEQ ID NO:523, SEQ ID NO:524, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:540, SEQ ID NO:541, SEQ ID NO:542, SEQ ID NO:543, SEQ ID NO:544, SEQ ID NO:545, SEQ ID NO:546, SEQ ID NO:547, SEQ ID NO:548, SEQ ID NO:549, SEQ ID NO:550, SEQ ID NO:551, SEQ ID NO:552, SEQ ID NO:553, SEQ ID NO:554, SEQ ID NO:555, SEQ ID NO:556, SEQ ID NO:557, SEQ ID NO:558, SEQ ID NO:559, SEQ ID NO:560, SEQ ID NO:561, SEQ ID NO:562, SEQ ID NO:563, SEQ ID NO:564, SEQ ID NO:565, SEQ ID NO:566, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:569, SEQ ID NO:570, SEQ ID NO:571, SEQ ID NO:572, SEQ ID NO:573, SEQ ID NO:574, SEQ ID NO:575, SEQ ID NO:576, SEQ ID NO:577, SEQ ID NO:578, SEQ ID NO:579, SEQ ID NO:580, SEQ ID NO:581, SEQ ID NO:582, SEQ ID NO:583, SEQ ID NO:584, SEQ ID NO:585, SEQ ID NO:586, SEQ ID NO:587, SEQ ID NO:588, SEQ ID NO:589, SEQ ID NO:590, SEQ ID NO:591, SEQ ID NO:592, SEQ ID NO:593, SEQ ID NO:594, SEQ ID NO:595, SEQ ID NO:596, SEQ ID NO:597, SEQ ID NO:598, SEQ ID NO:599, SEQ ID NO:600, SEQ ID NO:601, SEQ ID NO:602, SEQ ID NO:603, SEQ ID NO:604, SEQ ID NO:605, SEQ ID NO:606, SEQ ID NO:607, SEQ ID NO:608, SEQ ID NO:609, SEQ ID NO:610, SEQ ID NO:611, SEQ ID

NO:612, SEQ ID NO:613, SEQ ID NO:614, SEQ ID NO:615, SEQ ID NO:616, SEQ ID NO:617, SEQ ID NO:618, SEQ ID NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, SEQ ID NO:623, SEQ ID NO:624, SEQ ID NO:625;

or a complement of said sequence.

In other embodiments, the present invention provides an isolated polynucleotide consisting of a nucleotide sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ ID

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NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:540, SEQ ID NO:541, SEQ ID NO:542, SEQ ID NO:543, SEQ ID NO:544, SEQ ID NO:545, SEQ ID NO:546, SEQ ID NO:547, SEQ ID NO:548, SEQ ID NO:549, SEQ ID NO:550, SEQ ID NO:551, SEQ ID NO:552, SEQ ID NO:553, SEQ ID NO:554, SEQ ID NO:555, SEQ ID NO:556, SEQ ID NO:557, SEQ ID NO:558, SEQ ID NO:559, SEQ ID NO:560, SEQ ID NO:561, SEQ ID NO:562, SEQ ID NO:563, SEQ ID NO:564, SEQ ID NO:565, SEQ ID NO:566, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:569, SEQ ID NO:570, SEQ ID NO:571, SEQ ID NO:572, SEQ ID NO:573, SEQ ID NO:574, SEQ ID NO:575, SEQ ID NO:576, SEQ ID NO:577, SEQ ID NO:578, SEQ ID NO:579, SEQ ID NO:580, SEQ ID NO:581, SEQ ID NO:582, SEQ ID NO:583, SEQ ID NO:584, SEQ ID NO:585, SEQ ID NO:586, SEQ ID NO:587, SEQ ID NO:588, SEQ ID NO:589, SEQ ID NO:590, SEQ ID NO:591, SEQ ID NO:592, SEQ ID NO:593, SEQ ID NO:594, SEQ ID NO:595, SEQ ID NO:596, SEQ ID NO:597, SEQ ID NO:598, SEQ ID NO:599, SEQ ID NO:600, SEQ ID NO:601, SEQ ID NO:602, SEQ ID NO:603, SEQ ID NO:604, SEQ ID NO:605, SEQ ID NO:606, SEQ ID NO:607, SEQ ID NO:608, SEQ ID NO:609, SEQ ID NO:610, SEQ ID NO:611, SEQ ID NO:612, SEQ ID NO:613, SEQ ID NO:614, SEQ ID NO:615, SEQ ID NO:616, SEQ ID NO:617, SEQ ID NO:618, SEQ ID NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, SEQ ID NO:623, SEQ ID NO:624, SEQ ID NO:625;

or a complement of said sequence.

In further embodiments, the present invention provides an isolated polynucleotide consisting essentially of a nucleotide sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ

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or a complement of said sequence.

In yet other embodiments, the present invention provides an isolated polynucleotide comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID

NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO:245, SEQ ID NO:246, SEQ ID NO:247, SEQ ID NO:248, SEQ ID NO:249, SEQ ID NO:250, SEQ ID NO:251, SEQ ID NO:252, SEQ ID NO:253, SEQ ID NO:254, SEQ ID NO:255, SEQ ID NO:256, SEQ ID NO:257, SEQ ID NO:258, SEQ ID NO:259, SEQ ID NO:260, SEQ ID NO:261, SEQ ID NO:262, SEQ ID NO:263, SEQ ID NO:264, SEQ ID NO:265, SEQ ID NO:266, SEQ ID NO:267, SEQ ID NO:268, SEQ ID NO:269, SEQ ID NO:270, SEQ ID NO:271, SEQ ID NO:272, SEQ ID NO:273, SEQ ID NO:274, SEQ ID NO:275, SEQ ID NO:276, SEQ ID NO:277, SEQ ID NO:278, SEQ ID NO:279, SEQ ID NO:280, SEQ ID NO:281, SEQ ID NO:282, SEQ ID NO:283, SEQ ID NO:284, SEQ ID NO:285, SEQ ID NO:286, SEQ ID NO:287, SEQ ID NO:288, SEQ ID NO:289, SEQ ID NO:290, SEQ ID NO:291, SEQ ID NO:292, SEQ ID NO:293, SEQ ID NO:294, SEQ ID NO:295, SEQ ID NO:296, SEQ ID NO:297, SEQ ID NO:298, SEQ ID NO:299, SEQ ID NO:300, SEQ ID NO:301, SEQ ID NO:302, SEQ ID NO:303, SEQ ID NO:304, SEQ ID NO:305, SEQ ID NO:306, SEQ ID NO:307, SEQ ID NO:308, SEQ ID NO:309, SEQ ID NO:310, SEQ ID NO:311, SEQ ID NO:312, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:315, SEQ ID NO:316, SEQ ID NO:317, SEQ ID NO:318, SEQ ID NO:319, SEQ ID NO:320, SEQ ID NO:321, SEQ ID NO:322, SEQ ID NO:323, SEQ ID NO:324, SEQ ID NO:325, SEQ ID NO:326, SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:329, SEQ ID NO:330, SEQ ID NO:331, SEQ ID NO:332, SEQ ID NO:333, SEQ ID NO:334, SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO:338, SEQ ID NO:339, SEQ ID NO:340, SEQ ID NO:341, SEQ ID NO:342, SEQ ID NO:343, SEQ ID NO:344, SEQ ID NO:345, SEQ ID NO:346, SEQ ID NO:347, SEQ ID NO:348, SEQ ID NO:349, SEQ ID NO:350, SEQ ID NO:351, SEQ ID NO:352, SEQ ID NO:353, SEQ ID NO:354, SEQ ID NO:355, SEQ ID NO:356, SEQ ID NO:357, SEQ ID NO:358, SEQ ID NO:359, SEQ ID NO:360, SEQ ID NO:361, SEQ ID

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or to a complement of said sequence.

The invention also provides for proteins encoded by the above-described polynucleotides. In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions. Also provided by the present invention are organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein.

Processes are also provided for producing a protein, which comprise:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

(b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention, and/or a polynucleotide of the present invention, and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

The nucleotide sequences of the isolated cDNAs of the present invention are reported in the Sequence Listing below. Table 2 lists the "Clone ID Nos." assigned by applicants to each SEQ ID NO: in the Sequence Listing.

Table 2

Each pair of entries in this table consists of the SEQ ID NO (e.g., 1, 2, etc.) followed by the Clone ID No. for such sequence (e.g., YD123_1, YD124_1, etc.).

1	YD123_1	201	YD321_1	401	YE56_1	601	YH95_1
2	YD124_1	202	YD322_1	402	YE57_1	602	YH96_1
3	YD125_1	203	YD323_1	403	YE58_1	603	YH97_1
4	YD126_1	204	YD324_1	404	YE59_1	604	YH99_1
5	YD127_1	205	YD325_1	405	YE5_1	605	YH9_1
6	YD128_1	206	YD326_1	406	YE60_1	606	YHA2_1
7	YD129_1	207	YD327_1	407	YE61_1	607	YHA3_1
8	YD12_1	208	YD328_1	408	YE62_1	608	YHA4_1
9	YD130_1	209	YD329_1	409	YE63_1	609	YHA5_1
10	YD131_1	210	YD32_1	410	YE64_1	610	YHA6_1
11	YD132_1	211	YD330_1	411	YE65_1	611	YI101_1
12	YD133_1	212	YD331_1	412	YE66_1	612	YI102_1
13	YD134_1	213	YD332_1	413	YE67_1	613	YI103_1
14	YD135_1	214	YD333_1	414	YE68_1	614	YI104_1
15	YD136_1	215	YD334_1	415	YE69_1	615	YI106_1
16	YD138_1	216	YD335_1	416	YE6_1	616	YI107_1
17	YD139_1	217	YD336_1	417	YE70_1	617	YI108_1
18	YD13_1	218	YD337_1	418	YE71_1	618	YI109_1
19	YD140_1	219	YD338_1	419	YE73_1	619	YI10_1
20	YD142_1	220	YD339_1	420	YE74_1	620	YI110_1
21	YD143_1	221	YD33_1	421	YE75_1	621	YI111_1
22	YD144_1	222	YD340_1	422	YE76_1	622	YI112_1
23	YD146_1	223	YD341_1	423	YE77_1	623	YI113_1
24	YD147_1	224	YD342_1	424	YE79_1	624	YI114_1
25	YD148_1	225	YD343_1	425	YE80_1	625	YI115_1
26	YD149_1	226	YD344_1	426	YE81_1		

27	YD14_1	227	YD345_1	427	YE82_1
28	YD150_1	228	YD346_1	428	YE83_1
29	YD151_1	229	YD347_1	429	YE84_1
30	YD152_1	230	YD348_1	430	YE85_1
31	YD154_1	231	YD349_1	431	YE86_1
32	YD155_1	232	YD350_1	432	YE87_1
33	YD157_1	233	YD351_1	433	YE88_1
34	YD158_1	234	YD352_1	434	YE89_1
35	YD159_1	235	YD353_1	435	YE8_1
36	YD15_1	236	YD354_1	436	YE91_1
37	YD160_1	237	YD355_1	437	YE92_1
38	YD161_1	238	YD356_1	438	YE93_1
39	YD162_1	239	YD357_1	439	YE94_1
40	YD163_1	240	YD358_1	440	YE95_1
41	YD164_1	241	YD359_1	441	YE96_1
42	YD166_1	242	YD35_1	442	YE97_1
43	YD167_1	243	YD360_1	443	YE98_1
44	YD168_1	244	YD361_1	444	YE99_1
45	YD169_1	245	YD362_1	445	YE9_1
46	YD16_1	246	YD363_1	446	YEA2_1
47	YD170_1	247	YD364_1	447	YEA3_1
48	YD171_1	248	YD365_1	448	YF10_1
49	YD172_1	249	YD366_1	449	YF13_1
50	YD173_1	250	YD367_1	450	YF14_1
51	YD174_1	251	YD368_1	451	YF15_1
52	YD175_1	252	YD369_1	452	YF16_1
53	YD176_1	253	YD36_1	453	YF17_1
54	YD177_1	254	YD370_1	454	YF18_1
55	YD179_1	255	YD371_1	455	YF19_1
56	YD17_1	256	YD372_1	456	YF20_1
57	YD180_1	257	YD373_1	457	YF21_1
58	YD182_1	258	YD374_1	458	YF22_1
59	YD183_1	259	YD375_1	459	YF23_1
60	YD184_1	260	YD376_1	460	YF24_1
61	YD185_1	261	YD37_1	461	YF25_1
62	YD186_1	262	YD382_1	462	YF27_1
63	YD187_1	263	YD385_1	463	YF28_1

64	YD188_1	264	YD387_1	464	YF29_1
65	YD189_1	265	YD389_1	465	YF30_1
66	YD18_1	266	YD38_1	466	YF31_1
67	YD190_1	267	YD391_1	467	YF32_1
68	YD192_1	268	YD39_1	468	YF34_1
69	YD193_1	269	YD406_1	469	YF35_1
70	YD194_1	270	YD41_1	470	YF36_1
71	YD195_1	271	YD42_1	471	YF37_1
72	YD196_1	272	YD43_1	472	YF38_1
73	YD197_1	273	YD44_1	473	YF39_1
74	YD198_1	274	YD45_1	474	YF3_1
75	YD199_1	275	YD48_1	475	YF40_1
76	YD19_1	276	YD49_1	476	YF41_1
77	YD200_1	277	YD52_1	477	YF42_1
78	YD201_1	278	YD53_1	478	YF43_1
79	YD202_1	279	YD54_1	479	YF44_1
80	YD203_1	280	YD55_1	480	YF45_1
81	YD204_1	281	YD56_1	481	YF46_1
82	YD205_1	282	YD57_1	482	YF47_1
83	YD208_1	283	YD58_1	483	YF48_1
84	YD209_1	284	YD59_1	484	YF51_1
85	YD20_1	285	YD5_1	485	YF52_1
86	YD210_1	286	YD60_1	486	YF53_1
87	YD211_1	287	YD62_1	487	YF54_1
88	YD212_1	288	YD63_1	488	YF55_1
89	YD213_1	289	YD65_1	489	YF56_1
90	YD214_1	290	YD66_1	490	YF58_1
91	YD215_1	291	YD67_1	491	YF6_1
92	YD216_1	292	YD68_1	492	YF8_1
93	YD217_1	293	YD69_1	493	YFA1_1
94	YD219_1	294	YD6_1	494	YFA2_1
95	YD21_1	295	YD70_1	495	YFA3_1
96	YD221_1	296	YD71_1	496	YFA4_1
97	YD222_1	297	YD72_1	497	YFA5_1
98	YD223_1	298	YD74_1	498	YGA1_1
99	YD224_1	299	YD75_1	499	YGA2_1
100	YD225_1	300	YD76_1	500	YGA4_1

101	YD226_1	301	YD77_1	501	YH101_1
102	YD227_1	302	YD78_1	502	YH102_1
103	YD228_1	303	YD79_1	503	YH103_1
104	YD229_1	304	YD7_1	504	YH104_1
105	YD22_1	305	YD80_1	505	YH105_1
106	YD230_1	306	YD81_1	506	YH106_1
107	YD231_1	307	YD82_1	507	YH108_1
108	YD232_1	308	YD83_1	508	YH109_1
109	YD233_1	309	YD84_1	509	YH10_1
110	YD234_1	310	YD85_1	510	YH110_1
111	YD235_1	311	YD86_1	511	YH111_1
112	YD236_1	312	YD87_1	512	YH112_1
113	YD237_1	313	YD89_1	513	YH113_1
114	YD238_1	314	YD8_1	514	YH114_1
115	YD239_1	315	YD90_1	515	YH115_1
116	YD23_1	316	YD91_1	516	YH116_1
117	YD240_1	317	YD92_1	517	YH117_1
118	YD241_1	318	YD93_1	518	YH118_1
119	YD242_1	319	YD94_1	519	YH119_1
120	YD243_1	320	YD95_1	520	YH11_1
121	YD244_1	321	YD97_1	521	YH120_1
122	YD245_1	322	YD98_1	522	YH122_1
123	YD246_1	323	YD99_1	523	YH123_1
124	YD247_1	324	YD9_1	524	YH12_1
125	YD248_1	325	YDA10_1	525	YH13_1
126	YD249_1	326	YDA11_1	526	YH14_1
127	YD24_1	327	YDA12_1	527	YH15_1
128	YD250_1	328	YDA1_1	528	YH16_1
129	YD251_1	329	YDA2_1	529	YH17_1
130	YD252_1	330	YDA3_1	530	YH18_1
131	YD253_1	331	YDA4_1	531	YH19_1
132	YD254_1	332	YDA5_1	532	YH1_1
133	YD255_1	333	YDA6_1	533	YH21_1
134	YD256_1	334	YDA7_1	534	YH22_1
135	YD257_1	335	YE100_1	535	YH23_1
136	YD258_1	336	YE101_1	536	YH25_1
137	YD259_1	337	YE102_1	537	YH26_1

138	YD260_1	338	YE104_1	538	YH27_1
139	YD262_1	339	YE105_1	539	YH28_1
140	YD263_1	340	YE106_1	540	YH29_1
141	YD264_1	341	YE107_1	541	YH30_1
142	YD265_1	342	YE109_1	542	YH32_1
143	YD266_1	343	YE10_1	543	YH34_1
144	YD267_1	344	YE110_1	544	YH35_1
145	YD268_1	345	YE111_1	545	YH37_1
146	YD269_1	346	YE112_1	546	YH38_1
147	YD270_1	347	YE113_1	547	YH3_1
148	YD271_1	348	YE114_1	548	YH40_1
149	YD272_1	349	YE115_1	549	YH41_1
150	YD273_1	350	YE116_1	550	YH42_1
151	YD274_1	351	YE117_1	551	YH43_1
152	YD275_1	352	YE118_1	552	YH44_1
153	YD276_1	353	YE119_1	553	YH45_1
154	YD277_1	354	YE120_1	554	YH46_1
155	YD278_1	355	YE121_1	555	YH47_1
156	YD279_1	356	YE122_1	556	YH48_1
157	YD27_1	357	YE123_1	557	YH49_1
158	YD280_1	358	YE124_1	558	YH51_1
159	YD281_1	359	YE125_1	559	YH52_1
160	YD282_1	360	YE126_1	560	YH54_1
161	YD283_1	361	YE127_1	561	YH55_1
162	YD284_1	362	YE128_1	562	YH56_1
163	YD285_1	363	YE129_1	563	YH57_1
164	YD286_1	364	YE130_1	564	YH58_1
165	YD287_1	365	YE131_1	565	YH59_1
166	YD288_1	366	YE132_1	566	YH5_1
167	YD289_1	367	YE133_1	567	YH60_1
168	YD28_1	368	YE135_1	568	YH61_1
169	YD290_1	369	YE13_1	569	YH62_1
170	YD291_1	370	YE15_1	570	YH63_1
171	YD292_1	371	YE16_1	571	YH64_1
172	YD293_1	372	YE1_1	572	YH65_1
173	YD294_1	373	YE20_1	573	YH66_1
174	YD295_1	374	YE23_1	574	YH67_1

175	YD296_1	375	YE24_1	575	YH68_1
176	YD297_1	376	YE26_1	576	YH6_1
177	YD298_1	377	YE27_1	577	YH70_1
178	YD299_1	378	YE28_1	578	YH72_1
179	YD300_1	379	YE29_1	579	YH73_1
180	YD301_1	380	YE31_1	580	YH74_1
181	YD302_1	381	YE32_1	581	YH75_1
182	YD303_1	382	YE33_1	582	YH76_1
183	YD304_1	383	YE34_1	583	YH77_1
184	YD305_1	384	YE35_1	584	YH78_1
185	YD306_1	385	YE36_1	585	YH79_1
186	YD307_1	386	YE37_1	586	YH7_1
187	YD308_1	387	YE38_1	587	YH80_1
188	YD309_1	388	YE3_1	588	YH82_1
189	YD30_1	389	YE41_1	589	YH83_1
190	YD310_1	390	YE42_1	590	YH84_1
191	YD311_1	391	YE44_1	591	YH85_1
192	YD312_1	392	YE45_1	592	YH86_1
193	YD313_1	393	YE46_1	593	YH87_1
194	YD314_1	394	YE48_1	594	YH88_1
195	YD315_1	395	YE49_1	595	YH8_1
196	YD316_1	396	YE50_1	596	YH90_1
197	YD317_1	397	YE51_1	597	YH91_1
198	YD318_1	398	YE52_1	598	YH92_1
199	YD319_1	399	YE54_1	599	YH93_1
200	YD320_1	400	YE55_1	600	YH94_1

The "Clone ID No." for a particular clone consists of one or two letters followed by a number. The letters designate the tissue source from which the cDNA for that clone was isolated, and these sources are listed in Table 3 below.

TABLE 3

Sel.	Species	Stage	Tissue	Cell Type	Treatment
YD	Human	Adult	Brain	N/A	None
YDA	Human	Adult	Tonsil	Inflamed	None
YE	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
YEA	Human	Adult	Bladder	5637 carcinoma line	PMA + untreated
YF	Human	Fetal	Brain	19-23wks., M/F pool of 5	None

YFA	Human	Adult	Retina	WERI-Rb1 retinoblastoma line	None
YGA	Human	Adult	Bladder	5637 carcinoma line	PMA + untreated
YH	Human	Mixed	Brain	Fetal and adult brain	None
YHA	Human	Adult	Kidney	293 carcinoma line	None
YI	Human	Adult	Brain	N/A	None

<u>Table 3 Cell Type and Treatment Key:</u>
PMA: phorbol myristate acetate
PMA + untreated: Pool of PMA-treated and untreated cells

Thus, the tissue source for a particular cDNA sequence can be identified in Table 3 by the one and two letter designations used in the relevant "Clone ID No." in Table 2. For example, a cDNA clone designated as "YD123_1" would have been isolated from a human adult brain library (i.e., selection "YD") as indicated in Table 3.

As used herein, "polynucleotide" includes single- and double-stranded RNAs, DNAs and RNA:DNA hybrids.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology <u>10</u>, 773- 778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. <u>114</u>, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form(s) of such protein may be obtained by expression of the disclosed full-length polynucleotide

(preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence(s) of the mature form(s) of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

The chromosomal location corresponding to the polynucleotide sequences disclosed herein may also be determined, for example by hybridizing appropriately labeled polynucleotides of the present invention to chromosomes *in situ*. It may also be possible to determine the corresponding chromosomal location for a disclosed polynucleotide by identifying significantly similar nucleotide sequences in public databases, such as expressed sequence tags (ESTs), that have already been mapped to particular chromosomal locations. For at least some of the polynucleotide sequences disclosed herein, public database sequences having at least some similarity to the polynucleotide of the present invention have been listed by database accession number. Searches using the GenBank accession numbers of these public database sequences can then be performed at an Internet site provided by the National Center for Biotechnology Information having the address www.ncbi.nlm.nih.gov/UniGene, in order to identify "UniGene clusters" of overlapping sequences. Many of the "UniGene clusters" so identified will already have been mapped to particular chromosomal sites.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* 15(7): 250- 254; Lavarosky *et al.*, 1997, *Biochem. Mol. Med.* 62(1): 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the

gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, *Bioessays* 14(9): 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90(16): 7431-7435; Clark *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988, *Nature* 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence

identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

In particular, sequence identity may be determined using WU-BLAST (Washington University BLAST) version 2.0 software, which builds upon WU-BLAST version 1.4, which in turn is based on the public domain NCBI-BLAST version 1.4 (Altschul and Gish, 1996, Local alignment statistics, Doolittle *ed.*, *Methods in Enzymology* **266**: 460-480; Altschul *et al.*, 1990, Basic local alignment search tool, *Journal of Molecular Biology* **215**: 403-410; Gish and States, 1993, Identification of protein coding regions by database similarity search, *Nature Genetics* **3**: 266-272; Karlin and Altschul, 1993, Applications and statistics for multiple high-scoring segments in molecular sequences, *Proc. Natl. Acad. Sci. USA* **90**: 5873-5877; all of which are incorporated by reference herein). WU-BLAST version 2.0 executable programs for several UNIX platforms can be downloaded from the Internet file-transfer protocol (FTP) site ftp://blast.wustl.edu/blast/executables. The complete suite of search programs (BLASTP, BLASTN, BLASTX, TBLASTN, and TBLASTX) is provided at that site, in addition to several support programs. WU-BLAST 2.0 is copyrighted and may not be sold or redistributed in any form or manner without the express written consent of the author; but the posted executables may otherwise be freely used for commercial, nonprofit, or academic purposes. In all search programs in the suite -- BLASTP, BLASTN, BLASTX, TBLASTN and TBLASTX -- the gapped alignment routines are integral to the database search itself, and thus yield much better sensitivity and selectivity while producing the more easily interpreted output. Gapping can optionally be turned off in all of these programs, if desired. The default penalty (Q) for a gap of length one is Q=9 for proteins and BLASTP, and Q=10 for BLASTN, but may be changed to any integer value including zero, one through eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one through one hundred, etc. The default per-residue penalty for extending a gap (R) is R=2 for proteins and BLASTP, and R=10 for BLASTN, but may be changed to any integer value including zero, one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one through one hundred, etc. Any combination of values for Q and R can be used in order to align sequences so as to maximize overlap and identity while minimizing sequence gaps. The default amino acid comparison matrix is BLOSUM62, but other amino acid comparison matrices such as PAM can be utilized.

Species homologues of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide. Preferably, polynucleotide species homologues have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with

the given polynucleotide, and protein species homologues have at least 30% sequence identity (more preferably, at least 45% identity; most preferably at least 60% identity) with the given protein, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides or the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Species homologues may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species. Preferably, species homologues are those isolated from mammalian species. Most preferably, species homologues are those isolated from certain mammalian species such as, for example, *Pan troglodytes, Gorilla gorilla, Pongo pygmaeus, Hylobates concolor, Macaca mulatta, Papio papio, Papio hamadryas, Cercopithecus aethiops, Cebus capucinus, Aotus trivirgatus, Sanguinus oedipus, Microcebus murinus, Mus musculus, Rattus norvegicus, Cricetulus griseus, Felis catus, Mustela vison, Canis familiaris, Oryctolagus cuniculus, Bos taurus, Ovis aries, Sus scrofa,* and *Equus caballus,* for which genetic maps have been created allowing the identification of syntenic relationships between the genomic organization of genes in one species and the genomic organization of the related genes in another species (O'Brien and Seuánez, 1988, *Ann. Rev. Genet.* 22: 323-351; O'Brien *et al.*, 1993, *Nature Genetics* 3:103-112; Johansson *et al.*, 1995, *Genomics* 25: 682- 690; Lyons *et al.*, 1997, *Nature Genetics* 15: 47-56; O'Brien *et al.*, 1997, *Trends in Genetics* 13(10): 393-399; Carver and Stubbs, 1997, *Genome Research* 7:1123-1137; all of which are incorporated by reference herein).

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotides which also encode proteins which are identical or have significantly similar sequences to those encoded by the disclosed polynucleotides. Preferably, allelic variants have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with the given polynucleotide, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps. Allelic variants may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from individuals of the appropriate species.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides that hybridize under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at

least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M- R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp)‡	Hybridization Temperature and Buffer†	Wash Temperature and Buffer†
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T_B*; 1xSSC	T_B*; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T_D*; 1xSSC	T_D*; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T_F*; 1xSSC	T_F*; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T_H*; 4xSSC	T_H*; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T_J*; 4xSSC	T_J*; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T_L*; 2xSSC	T_L*; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T_N*; 6xSSC	T_N*; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T_P*; 6xSSC	T_P*; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T_R*; 4xSSC	T_R*; 4xSSC

‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

†: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6($\log_{10}$[Na^+]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na^+] is the concentration of sodium ions in the hybridization buffer ([Na^+] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may contain sequences at its 5′ and/or 3′ end that are derived from linker, polylinker, or multiple cloning site sequences commonly found in vectors such as the pMT2 or pED expression vectors (see below). For example, sequences such as SEQ ID NO:626, SEQ ID NO:627, or SEQ ID NO:628 may be found at the 5′ end of an isolated polynucleotide of the invention, or the complement of any of these sequences may be found at its 3′ end. Similarly, sequences such as SEQ ID NO:629, SEQ ID NO:630, or SEQ ID NO:631 may be found at the 3′ end of an isolated polynucleotide of the invention, or the complement of any of these sequences may be found at its 5′ end. In addition, variants of these linker sequences may be present in isolated polynucleotides of the invention, which linker variants vary from SEQ ID NO:626 through SEQ ID NO:631 by the alteration, insertion, or deletion of one or more nucleotides. Therefore, a preferred embodiment of the invention comprises the nucleotide sequence of any of the isolated polynucleotides disclosed herein, beginning at nucleotide 25 and ending at nucleotide (N-25) of the SEQ ID NO for that polynucleotide, where N represents the total number of nucleotides in the sequence. As a specific example, a preferred embodiment of the invention comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 25 to nucleotide 802, where the total number of nucleotides (N) in SEQ ID NO:1 is 827, and N-25 equals 802. More preferably, a polynucleotide of the invention comprises the nucleotide sequence of any of the isolated polynucleotides disclosed herein, beginning at nucleotide 30 and ending at nucleotide (N-30) of the SEQ ID NO for that polynucleotide. Most preferably, a polynucleotide of the invention comprises the nucleotide sequence of any of the isolated polynucleotides disclosed herein, beginning at nucleotide 35 and ending at nucleotide (N-35) of the SEQ ID NO for that polynucleotide. Similarly, additional embodiments are those nucleotide sequences that extend from nucleotide 40 to nucleotide (N-40), or from nucleotide

45 to nucleotide (N-45), or from nucleotide 50 to nucleotide (N-50), or from nucleotide 60 to nucleotide (N-60), or from nucleotide 65 to nucleotide (N-65), or from nucleotide 70 to nucleotide (N-70), or from nucleotide 75 to nucleotide (N- 75), or from nucleotide 80 to nucleotide (N-80), etc., for any of the polynucleotides disclosed herein. Further preferred embodiments are those nucleotide sequences that are subsequences of the nucleotide sequences disclosed herein, beginning at any nucleotide position selected from the group consisting of nucleotide 5, nucleotide 10, nucleotide 15, nucleotide 20, nucleotide 25, nucleotide 30, nucleotide 35, nucleotide 40, nucleotide 45, nucleotide 50, nucleotide 55, nucleotide 60, nucleotide 65, nucleotide 70, nucleotide 75, or nucleotide 80, and ending at any nucleotide position selected from the group consisting of nucleotide (N-5), nucleotide (N-10), nucleotide (N-15), nucleotide (N-20), nucleotide (N-25), nucleotide (N-30), nucleotide (N-35), nucleotide (N-40), nucleotide (N-45), nucleotide (N-50), nucleotide (N-55), nucleotide (N-60), nucleotide (N-65), nucleotide (N-70), nucleotide (N-75), or nucleotide (N-80), wherein N is the total number of nucleotides disclosed for a particular SEQ ID NO.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida,* or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium,* or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by

phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin- toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLabs (Beverly, MA), Pharmacia (Piscataway, NJ) and Invitrogen Corporation (Carlsbad, CA), respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from the Eastman Kodak Company (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The primary use of polynucleotides of the invention which are sESTs is as porbes for the identification and isolation of full- length cDNAs and genomic DNA molecules which correspond (i.e., is a longer polynucleotide sequence of which substantially the entire sEST is a fragment in the case of a full-length cDNA, or which encodes the sEST in the case of a genomic DNA molecule) to such sESTs. Techniques for use of such sequences as probes for larger cDNAs or genomic molecules are well known in the art.

The polynucleotides can also be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract- out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high- throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction.

Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1- 3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli

et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

<u>Immune Stimulating or Suppressing Activity</u>

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies

and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen- specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The

administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.,* B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.,* Science *257*:789-792 (1992) and Turka *et al.,* Proc. Natl. Acad. Sci USA, *89*:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine

experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor- specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1- like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be

transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7,

Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to

platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in- vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells.* R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells.* R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells.* R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells.* R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells.* R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic

disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779- 782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of

cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs

involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such

as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as

M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form,

the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 μg to about 100 mg (preferably about 0.1ng to about 10 mg, more preferably about 0.1 μg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for

synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well- defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl- methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

What is claimed is:

1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID

NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO:245, SEQ ID NO:246, SEQ ID NO:247, SEQ ID NO:248, SEQ ID NO:249, SEQ ID NO:250, SEQ ID NO:251, SEQ ID NO:252, SEQ ID NO:253, SEQ ID NO:254, SEQ ID NO:255, SEQ ID NO:256, SEQ ID NO:257, SEQ ID NO:258, SEQ ID NO:259, SEQ ID NO:260, SEQ ID NO:261, SEQ ID NO:262, SEQ ID NO:263, SEQ ID NO:264, SEQ ID NO:265, SEQ ID NO:266, SEQ ID NO:267, SEQ ID NO:268, SEQ ID NO:269, SEQ ID NO:270, SEQ ID NO:271, SEQ ID NO:272, SEQ ID NO:273, SEQ ID NO:274, SEQ ID NO:275, SEQ ID NO:276, SEQ ID NO:277, SEQ ID NO:278, SEQ ID NO:279, SEQ ID NO:280, SEQ ID NO:281, SEQ ID NO:282, SEQ ID NO:283, SEQ ID NO:284, SEQ ID NO:285, SEQ ID NO:286, SEQ ID NO:287, SEQ ID NO:288, SEQ ID NO:289, SEQ ID NO:290, SEQ ID NO:291, SEQ ID NO:292, SEQ ID NO:293, SEQ ID NO:294, SEQ ID NO:295, SEQ ID NO:296, SEQ ID NO:297, SEQ ID NO:298, SEQ ID NO:299, SEQ ID NO:300, SEQ ID NO:301, SEQ ID NO:302, SEQ ID NO:303, SEQ ID NO:304, SEQ ID NO:305, SEQ ID NO:306, SEQ ID NO:307, SEQ ID NO:308, SEQ ID NO:309, SEQ ID NO:310, SEQ ID NO:311, SEQ ID NO:312, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:315, SEQ ID NO:316, SEQ ID NO:317, SEQ ID NO:318, SEQ ID NO:319, SEQ ID NO:320, SEQ ID NO:321, SEQ ID NO:322, SEQ ID NO:323, SEQ ID NO:324, SEQ ID NO:325, SEQ ID NO:326, SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:329, SEQ ID NO:330, SEQ ID NO:331, SEQ ID NO:332, SEQ ID NO:333, SEQ ID NO:334, SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO:338, SEQ ID NO:339, SEQ ID NO:340, SEQ ID NO:341, SEQ ID NO:342, SEQ ID NO:343, SEQ ID NO:344, SEQ ID NO:345, SEQ ID NO:346, SEQ ID NO:347, SEQ ID NO:348, SEQ ID NO:349, SEQ ID NO:350, SEQ ID NO:351, SEQ ID NO:352, SEQ ID NO:353, SEQ ID NO:354, SEQ ID NO:355, SEQ ID NO:356, SEQ ID

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NO:542, SEQ ID NO:543, SEQ ID NO:544, SEQ ID NO:545, SEQ ID NO:546, SEQ ID NO:547, SEQ ID NO:548, SEQ ID NO:549, SEQ ID NO:550, SEQ ID NO:551, SEQ ID NO:552, SEQ ID NO:553, SEQ ID NO:554, SEQ ID NO:555, SEQ ID NO:556, SEQ ID NO:557, SEQ ID NO:558, SEQ ID NO:559, SEQ ID NO:560, SEQ ID NO:561, SEQ ID NO:562, SEQ ID NO:563, SEQ ID NO:564, SEQ ID NO:565, SEQ ID NO:566, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:569, SEQ ID NO:570, SEQ ID NO:571, SEQ ID NO:572, SEQ ID NO:573, SEQ ID NO:574, SEQ ID NO:575, SEQ ID NO:576, SEQ ID NO:577, SEQ ID NO:578, SEQ ID NO:579, SEQ ID NO:580, SEQ ID NO:581, SEQ ID NO:582, SEQ ID NO:583, SEQ ID NO:584, SEQ ID NO:585, SEQ ID NO:586, SEQ ID NO:587, SEQ ID NO:588, SEQ ID NO:589, SEQ ID NO:590, SEQ ID NO:591, SEQ ID NO:592, SEQ ID NO:593, SEQ ID NO:594, SEQ ID NO:595, SEQ ID NO:596, SEQ ID NO:597, SEQ ID NO:598, SEQ ID NO:599, SEQ ID NO:600, SEQ ID NO:601, SEQ ID NO:602, SEQ ID NO:603, SEQ ID NO:604, SEQ ID NO:605, SEQ ID NO:606, SEQ ID NO:607, SEQ ID NO:608, SEQ ID NO:609, SEQ ID NO:610, SEQ ID NO:611, SEQ ID NO:612, SEQ ID NO:613, SEQ ID NO:614, SEQ ID NO:615, SEQ ID NO:616, SEQ ID NO:617, SEQ ID NO:618, SEQ ID NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, SEQ ID NO:623, SEQ ID NO:624, SEQ ID NO:625;

or a complement of said sequence.

2. An isolated polynucleotide consisting of a nucleotide sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID

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or a complement of said sequence.

3. An isolated polynucleotide comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID

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or to a complement of said sequence.

4. The polynucleotide of any one of claims 1-3, wherein said polynucleotide is operably linked to at least one expression control sequence.

5. A vector comprising the polynucleotide of claim 4.

6. A host cell transformed with a vector comprising the polynucleotide of any one of claims 1-3.

7. A process for producing a protein encoded by the polynucleotide of claim 4, which process comprises:

(a) growing a culture of a host cell in a suitable culture medium, wherein the host cell has been transformed with the polynucleotide of claim 4; and

(b) purifying said protein from the culture.

8. A protein produced according to the process of claim 7.

9. An antibody that specifically binds to the protein of claim 8.

10. A method for detecting the protein of claim 8, comprising contacting a sample suspected of containing the protein with an antibody that specifically binds to the protein, under conditions such that the antibody binds the protein and the protein is detected.

11. A method for detecting the polynucleotide of any one of claims 1-3, comprising contacting a sample suspected of containing the polynucleotide with a polynucleotide reagent that hybridizes to the polynucleotide, under conditions such that the reagent binds the polynucleotide and the polynucleotide is detected.

12. The method of claim 10, wherein the sample is a biological sample.

13. The method of claim 12, where the biological sample is isolated from a human.

14. The method of claim 11, wherein the sample is a biological sample.

15. The method of claim 14, where the biological sample is isolated from a human.

16. A method of identifying a compound that modulates the activity of the protein of claim 8, comprising contacting a composition comprising the protein with a test compound and monitoring the effect of the test compound on the activity of the protein, such that a modulatory compound is identified.

17. A method of identifying a compound that modulates the expression of the polynucleotide of any one of claims 1-3, comprising contacting a cell that expresses the polynucleotide with a test compound and determining the effect of the test compound on the expression of the polynucleotide, such that a modulatory compound is identified.

18. A method of identifying a compound that modulates the production of the protein of claim 8, comprising contacting a cell that produces the protein with the test compound and determining the effect of the test compound on the production of the protein, such that a modulatory compound is identified.

19. A method of treating a subject having a disorder characterized by aberrant expression of the polynucleotide of any one of claims 1-3, comprising administering to said subject a therapeutically effective amount of a compound that modulates expression of the polypeptide, such that treatment is effected.

20. A method of treating a subject having a disorder characterized by aberrant production of the protein of claim 8, comprising administering to said subject a therapeutically effective amount of a compound that modulates production of the protein, such that treatment is effected.

21. A method of treating a subject having a disorder characterized by aberrant activity of the protein of claim 8, comprising administering to said subject a therapeutically effective amount of a compound that modulates activity of the protein, such that treatment is effected.

SEQUENCE LISTING

<110> Wong, Gordon G.
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Agostino, Michael J.
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Gulukota, Kamalakar
Graham, James R.
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<212> DNA
<213> Homo sapiens

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<212> DNA
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<210> 13
<211> 589
<212> DNA
<213> Homo sapiens

<400> 13
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<211> 779
<212> DNA
<213> Homo sapiens

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<211> 415
<212> DNA
<213> Homo sapiens

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<210> 16
<211> 436
<212> DNA
<213> Homo sapiens

<400> 16
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<210> 17
<211> 743
<212> DNA

<213> Homo sapiens

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<210> 18
<211> 785
<212> DNA
<213> Homo sapiens

<400> 18
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<211> 434
<212> DNA
<213> Homo sapiens

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<211> 920
<212> DNA
<213> Homo sapiens

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<211> 757
<212> DNA
<213> Homo sapiens

<400> 21
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<210> 22
<211> 386
<212> DNA
<213> Homo sapiens

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<211> 622
<212> DNA
<213> Homo sapiens

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<210> 24
<211> 514
<212> DNA
<213> Homo sapiens

<400> 24
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<211> 884
<212> DNA
<213> Homo sapiens

<400> 25
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<210> 26
<211> 408
<212> DNA
<213> Homo sapiens

<400> 26
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<210> 27
<211> 483
<212> DNA
<213> Homo sapiens

<400> 27
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<210> 28
<211> 652
<212> DNA
<213> Homo sapiens

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<210> 29
<211> 510
<212> DNA
<213> Homo sapiens

<400> 29
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<210> 30
<211> 743
<212> DNA
<213> Homo sapiens

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<210> 31
<211> 790
<212> DNA
<213> Homo sapiens

<400> 31

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<211> 652
<212> DNA
<213> Homo sapiens

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<210> 33
<211> 827
<212> DNA
<213> Homo sapiens

<400> 33
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<210> 34
<211> 689
<212> DNA
<213> Homo sapiens

<400> 34
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<210> 35
<211> 627
<212> DNA
<213> Homo sapiens

<400> 35
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accatattga ataaatgtga tcaagcc 627

<210> 36
<211> 595
<212> DNA
<213> Homo sapiens

<400> 36
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<210> 37
<211> 702
<212> DNA
<213> Homo sapiens

<400> 37
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gtgcaggagg aaactaacag ttcagtaaac tctgccttga cc 702

<210> 38

<211> 719
<212> DNA
<213> Homo sapiens

<400> 38
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<210> 39
<211> 463
<212> DNA
<213> Homo sapiens

<400> 39
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<210> 40
<211> 377
<212> DNA
<213> Homo sapiens

<400> 40
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<210> 41
<211> 645
<212> DNA
<213> Homo sapiens

<400> 41
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<210> 42
<211> 900
<212> DNA
<213> Homo sapiens

<400> 42
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<210> 43
<211> 552
<212> DNA
<213> Homo sapiens

<400> 43
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<210> 44
<211> 728
<212> DNA
<213> Homo sapiens

<400> 44
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<210> 45
<211> 367
<212> DNA
<213> Homo sapiens

<400> 45
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<210> 46
<211> 664
<212> DNA
<213> Homo sapiens

<400> 46
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<210> 47
<211> 839
<212> DNA
<213> Homo sapiens

<400> 47
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<210> 48
<211> 683
<212> DNA
<213> Homo sapiens

<400> 48
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<210> 49
<211> 601
<212> DNA
<213> Homo sapiens

<400> 49
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<210> 50
<211> 412
<212> DNA
<213> Homo sapiens

<400> 50
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<213> Homo sapiens

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cccc 664

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<212> DNA
<213> Homo sapiens

<400> 52
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<211> 879
<212> DNA
<213> Homo sapiens

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<211> 773
<212> DNA
<213> Homo sapiens

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<210> 55
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<212> DNA
<213> Homo sapiens

<400> 55
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<211> 380
<212> DNA
<213> Homo sapiens

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<210> 57
<211> 767
<212> DNA
<213> Homo sapiens

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<211> 358
<212> DNA
<213> Homo sapiens

<400> 58
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<210> 59
<211> 517
<212> DNA
<213> Homo sapiens

<400> 59
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<210> 60
<211> 386
<212> DNA
<213> Homo sapiens

<400> 60
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ctgggaaacg ggcgcggcc ggaaag 386

<210> 61
<211> 428
<212> DNA
<213> Homo sapiens

<400> 61
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<211> 557
<212> DNA
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<210> 63
<211> 824
<212> DNA
<213> Homo sapiens

<400> 63
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<211> 570
<212> DNA
<213> Homo sapiens

<400> 64
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<210> 65
<211> 424
<212> DNA
<213> Homo sapiens

<400> 65
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gttg 424

<210> 66
<211> 467
<212> DNA
<213> Homo sapiens

<400> 66
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<210> 67
<211> 395
<212> DNA
<213> Homo sapiens

<400> 67
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<210> 68
<211> 780
<212> DNA
<213> Homo sapiens

<400> 68
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<210> 69
<211> 698
<212> DNA
<213> Homo sapiens

<400> 69
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<210> 70
<211> 567
<212> DNA
<213> Homo sapiens

<400> 70
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<210> 71
<211> 527
<212> DNA
<213> Homo sapiens

<400> 71
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<210> 72
<211> 427
<212> DNA
<213> Homo sapiens

<400> 72
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<210> 73
<211> 817
<212> DNA
<213> Homo sapiens

<400> 73
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<210> 74
<211> 511
<212> DNA
<213> Homo sapiens

<400> 74
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<210> 75
<211> 792
<212> DNA

<213> Homo sapiens

<400> 75
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<210> 76
<211> 452
<212> DNA
<213> Homo sapiens

<400> 76
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ttggagtaag aagaggatta aaaaggaaag ac 452

<210> 77
<211> 442
<212> DNA
<213> Homo sapiens

<400> 77
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<210> 78
<211> 704
<212> DNA
<213> Homo sapiens

<400> 78
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<210> 79
<211> 644
<212> DNA
<213> Homo sapiens

<400> 79
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<210> 80
<211> 396
<212> DNA
<213> Homo sapiens

<400> 80
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<210> 81
<211> 852
<212> DNA
<213> Homo sapiens

<400> 81
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<210> 82
<211> 651
<212> DNA
<213> Homo sapiens

<400> 82
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<210> 83
<211> 892
<212> DNA
<213> Homo sapiens

<400> 83

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<210> 84
<211> 469
<212> DNA
<213> Homo sapiens

<400> 84

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gctgttgccc gcgcaggtgg ccgcgtgcgc acagaccgtg gtgagcttg            469
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<210> 85
<211> 791
<212> DNA
<213> Homo sapiens

<400> 85

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gggcaaggac acgnactact tcatcaagac caccacggcc gagagcgacc tgggcacgnt 780
gcggttgatc a 791

<210> 86
<211> 770
<212> DNA
<213> Homo sapiens

<400> 86
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<210> 87
<211> 800
<212> DNA
<213> Homo sapiens

<400> 87
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<210> 88
<211> 861
<212> DNA
<213> Homo sapiens

<400> 88
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<210> 89
<211> 636
<212> DNA
<213> Homo sapiens

<400> 89
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<210> 90
<211> 827
<212> DNA
<213> Homo sapiens

<400> 90
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<210> 91
<211> 672
<212> DNA
<213> Homo sapiens

<400> 91
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<213> Homo sapiens

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<212> DNA
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<211> 478
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<212> DNA
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<212> DNA
<213> Homo sapiens

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<212> DNA
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<210> 108
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<212> DNA
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<212> DNA
<213> Homo sapiens

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<212> DNA
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<211> 881
<212> DNA
<213> Homo sapiens

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<211> 813
<212> DNA
<213> Homo sapiens

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<211> 604
<212> DNA
<213> Homo sapiens

<400> 113
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<211> 541
<212> DNA
<213> Homo sapiens

<400> 114
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<211> 565
<212> DNA
<213> Homo sapiens

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<210> 116
<211> 894
<212> DNA
<213> Homo sapiens

<400> 116
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<210> 117
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<212> DNA
<213> Homo sapiens

<400> 117
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<210> 118
<211> 799
<212> DNA
<213> Homo sapiens

<400> 118
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gtgtttctca ggacttaat 799

<210> 119
<211> 375
<212> DNA
<213> Homo sapiens

<400> 119
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ccctgggccg aggag 375

<210> 120
<211> 649
<212> DNA
<213> Homo sapiens

<400> 120
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<210> 121
<211> 761
<212> DNA
<213> Homo sapiens

<400> 121
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<210> 122
<211> 369
<212> DNA
<213> Homo sapiens

<400> 122
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tgctctcnta atgaagacat agccgattct ctgcccgggc cccttgctga tgctcctccg 180
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aatatttt 369

<210> 123
<211> 867
<212> DNA
<213> Homo sapiens

<400> 123
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aggaggtttt gcccaccagg gggcagcaga gggtcaggga gcaatgggcc ctgggtggag 180
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aagatagttg ctatttggga agaaacg 867

<210> 124
<211> 694
<212> DNA
<213> Homo sapiens

<400> 124
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tccagcctgg gtgacagagc gagactccat ctct 694

<210> 125
<211> 787
<212> DNA
<213> Homo sapiens

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<210> 126
<211> 880
<212> DNA
<213> Homo sapiens

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<210> 127
<211> 460
<212> DNA
<213> Homo sapiens

<400> 127
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<210> 128
<211> 495
<212> DNA
<213> Homo sapiens

<400> 128
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<211> 557
<212> DNA
<213> Homo sapiens

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<210> 130
<211> 600
<212> DNA
<213> Homo sapiens

<400> 130
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<210> 131
<211> 455
<212> DNA
<213> Homo sapiens

<400> 131
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<210> 132
<211> 691
<212> DNA
<213> Homo sapiens

<400> 132
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<210> 133
<211> 497
<212> DNA
<213> Homo sapiens

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<210> 134

<211> 834
<212> DNA
<213> Homo sapiens

<400> 134
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gctgctccct gtttctggag ctggatgttc cccagctggc agttgagctg cctgagccaa 780
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<211> 814
<212> DNA
<213> Homo sapiens

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<210> 136
<211> 457
<212> DNA
<213> Homo sapiens

<400> 136
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<210> 137
<211> 813
<212> DNA
<213> Homo sapiens

<400> 137
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tccggcctga gtgacagggt gggcctccgt ttc 813

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<212> DNA
<213> Homo sapiens

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<210> 139
<211> 727
<212> DNA
<213> Homo sapiens

<400> 139
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<210> 140
<211> 812
<212> DNA
<213> Homo sapiens

<400> 140
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aggagaaaca ttgtatgtca tagaggaaga caaaggcgat ggctggaccc gcattcggag 720
aaatgaagat gaagagggtt atgtccccac ttcatatgtc gaagtctgtt tggacaaaaa 780
tgccaaaggt gctaagactt atatttaata cc 812

<210> 141
<211> 621
<212> DNA
<213> Homo sapiens

<400> 141
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ggactcggga gtgagagatt gcagtgagcc gagatcatgc cgctgcactc caacctgggt 600
gtcagagcga gactctgtct c 621

<210> 142
<211> 572
<212> DNA
<213> Homo sapiens

<400> 142
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<210> 143
<211> 709
<212> DNA
<213> Homo sapiens

<400> 143
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<210> 144

<211> 851
<212> DNA
<213> Homo sapiens

<400> 144
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<210> 145
<211> 422
<212> DNA
<213> Homo sapiens

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<210> 146
<211> 555
<212> DNA
<213> Homo sapiens

<400> 146
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<210> 147
<211> 513
<212> DNA
<213> Homo sapiens

<400> 147
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ccaagacttc caataaaacg tgcgttcctc tcg 513

<210> 148
<211> 801
<212> DNA
<213> Homo sapiens

<400> 148
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<210> 149
<211> 503
<212> DNA
<213> Homo sapiens

<400> 149
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ccgccagcgc tcccagaccg ttacctagcc cagcgcccga aagccgtctc ttctatgcaa 420
taacacaata gtattactct actgcgatgt acggaactgc ggtgtgtgta cacatactca 480
cgtatatgca catatttata tac 503

<210> 150
<211> 485
<212> DNA
<213> Homo sapiens

<400> 150
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<210> 151
<211> 723
<212> DNA
<213> Homo sapiens

<400> 151

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ccc 723

<210> 152
<211> 697
<212> DNA
<213> Homo sapiens

<400> 152
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<211> 456
<212> DNA
<213> Homo sapiens

<400> 153
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gcccttcgtc ctgggaaacg gggcgcggcc ggaaag 456

<210> 154
<211> 377
<212> DNA
<213> Homo sapiens

<400> 154
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gcctctttgt gagcctc 377

<210> 155
<211> 609

<212> DNA
<213> Homo sapiens

<400> 155
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ggccccgcc 609

<210> 156
<211> 587
<212> DNA
<213> Homo sapiens

<400> 156
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<210> 157
<211> 651
<212> DNA
<213> Homo sapiens

<400> 157
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<210> 158
<211> 745
<212> DNA
<213> Homo sapiens

<400> 158
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gcttgagccc ggagggtgga ggttgcagtg agccaagatc acgccactnc actccngctt 720
gggtgataga gcacgactct atctc 745

<210> 159
<211> 668
<212> DNA
<213> Homo sapiens

<400> 159
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agtcaccc 668

<210> 160
<211> 375
<212> DNA
<213> Homo sapiens

<400> 160
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ctgtgccgct gcaggtgtct cctgcacctg cgccagctcc tgcaagtgca aagagtgcaa 120
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<210> 161
<211> 774
<212> DNA
<213> Homo sapiens

<400> 161
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<210> 162
<211> 712
<212> DNA
<213> Homo sapiens

<400> 162
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<210> 163
<211> 876
<212> DNA
<213> Homo sapiens

<400> 163
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<210> 164
<211> 410
<212> DNA
<213> Homo sapiens

<400> 164
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<210> 165
<211> 628
<212> DNA
<213> Homo sapiens

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<210> 166
<211> 520
<212> DNA
<213> Homo sapiens

<400> 166
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<210> 167
<211> 676
<212> DNA
<213> Homo sapiens

<400> 167
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<210> 168
<211> 691
<212> DNA
<213> Homo sapiens

<400> 168
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<210> 169
<211> 693
<212> DNA
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<400> 169
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<211> 681
<212> DNA
<213> Homo sapiens

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tcccctaccc tgggccagcg gcccccactt ccttgtcctc tggcggtggc aggtgcccct 660
cctcaagcag tgccacagaa a 681

<210> 171
<211> 798
<212> DNA
<213> Homo sapiens

<400> 171
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attaaaagaa attacccc 798

<210> 172
<211> 697
<212> DNA
<213> Homo sapiens

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<210> 173
<211> 735
<212> DNA
<213> Homo sapiens

<400> 173
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<211> 664
<212> DNA
<213> Homo sapiens

<400> 174
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ttcc 664

<210> 175
<211> 829
<212> DNA
<213> Homo sapiens

<400> 175
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<210> 176
<211> 827
<212> DNA
<213> Homo sapiens

<400> 176
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<211> 1305
<212> DNA
<213> Homo sapiens

<400> 177
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<211> 907
<212> DNA
<213> Homo sapiens

<400> 178
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<210> 179
<211> 770
<212> DNA
<213> Homo sapiens

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<211> 745
<212> DNA
<213> Homo sapiens

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agaaggagga cttcccactg ccggt 745

<210> 181
<211> 891
<212> DNA
<213> Homo sapiens

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<211> 599
<212> DNA
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<211> 941
<212> DNA
<213> Homo sapiens

<400> 183
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<211> 785
<212> DNA
<213> Homo sapiens

<400> 184
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<212> DNA
<213> Homo sapiens

<400> 185
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aagaagtcaa ggcccctccc gcaaatgtgt accccctgccc gcgccactgc accccgccgc 240
acccccacct cccccggggg ccctgctgcg gatgccggag tgggagagtc tctgagctgt 300
gagattgatc ttgcccctaa ttggagagga agccgggcgc caagacacac ggggctcctg 360
ccttgggagc cagggcc 377

<210> 186
<211> 848
<212> DNA
<213> Homo sapiens

<400> 186
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gcaatggtct ggccctgcgt ggagcccagg ccaggccccc ggttgaccgt ctggcggatg 840
cgcaggaa 848

<210> 187
<211> 644
<212> DNA
<213> Homo sapiens

<400> 187
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cccaccctgg gtattcaaaa acggcagaca caacatgttc ctcc 644

<210> 188
<211> 849

<212> DNA
<213> Homo sapiens

<400> 188
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gggccagggc cccacacacc cgagaccctc aggggcagca ggagggacgg ggccagggca 180
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cccggtccc 849

<210> 189
<211> 686
<212> DNA
<213> Homo sapiens

<400> 189
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acagatgaca tccttgtggc ctcagcagag tgtcccagcg atgatgagga cattgacccc 180
tgtgagccga gctcagccaa cccaacccga gcaggcggca gagagccgta tccaggctca 240
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gctgttgtaa aggagaaaca acccagaagt gcgaaaagct ccaacaaaaa taagaaaaac 480
aaggataaag agtattatgt ctgatcccaa gatcttaaat ggacacttgt atagaaatag 540
tcttcatttt atctgagaca taatataaac ttatttactt tcctttttat gaagcacata 600
caaaagaaga cagagaatgc aatcaggaag gaaagacttt ttaaaaaata aaaacaagta 660
tctcatgctc ttgtttctcc aaaaag 686

<210> 190
<211> 782
<212> DNA
<213> Homo sapiens

<400> 190
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ggaggcccag gtctccgtgc agcccaactt ccagcaggac aagttcctgg ggcgctggtt 180
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gtgaccccca cgctctggat gtctctgctc tgttccttcc ccgagcccct gccccggctc 720
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tc 782

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<212> DNA
<213> Homo sapiens

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<210> 192
<211> 774
<212> DNA
<213> Homo sapiens

<400> 192
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cgactacgac cagtacgcgc tgctgtacag ccagggcagc aagggccctg gcgaggactt 480
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<210> 193
<211> 771
<212> DNA
<213> Homo sapiens

<400> 193
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<210> 194
<211> 835
<212> DNA
<213> Homo sapiens

<400> 194
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<210> 195
<211> 602
<212> DNA
<213> Homo sapiens

<400> 195
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ac 602

<210> 196
<211> 835
<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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gg 842

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<211> 749
<212> DNA
<213> Homo sapiens

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<210> 199
<211> 440
<212> DNA
<213> Homo sapiens

<400> 199
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atccgtacta tacttcacaa caatcctaat cctaatacca actatctccc taattgaaaa 420
caaaatactc aaatgggcct 440

<210> 200
<211> 829
<212> DNA
<213> Homo sapiens

<400> 200
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agatttggac acacagtgga gcccctttac agaaacggcc tctcggcgg 829

<210> 201
<211> 459
<212> DNA
<213> Homo sapiens

<400> 201
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<210> 202
<211> 388
<212> DNA
<213> Homo sapiens

<400> 202
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tgctccgtgt gaataaatgc ccagtggc 388

<210> 203
<211> 646
<212> DNA
<213> Homo sapiens

<400> 203
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<211> 618
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<213> Homo sapiens

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<212> DNA
<213> Homo sapiens
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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

<400> 207
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gtgg 784

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<211> 792
<212> DNA
<213> Homo sapiens

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<210> 209
<211> 373
<212> DNA
<213> Homo sapiens

<400> 209
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gcagggcagc ccc 373

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<211> 827
<212> DNA
<213> Homo sapiens

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<210> 211
<211> 606
<212> DNA
<213> Homo sapiens

<400> 211
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<210> 212
<211> 588
<212> DNA
<213> Homo sapiens

<400> 212

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<210> 213
<211> 894
<212> DNA
<213> Homo sapiens

<400> 213

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<210> 214
<211> 383
<212> DNA
<213> Homo sapiens

<400> 214

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cagccattaa attataaatc tgg                                         383
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<210> 215

<211> 644
<212> DNA
<213> Homo sapiens

<400> 215
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atgcggaaga aggcaagaga gaaggaggac ttcccactgc cggt 644

<210> 216
<211> 892
<212> DNA
<213> Homo sapiens

<400> 216
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<210> 217
<211> 792
<212> DNA
<213> Homo sapiens

<400> 217
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<210> 218
<211> 520
<212> DNA
<213> Homo sapiens

<400> 218
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<210> 219
<211> 797
<212> DNA
<213> Homo sapiens

<400> 219
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<210> 220
<211> 809
<212> DNA
<213> Homo sapiens

<400> 220
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<211> 445
<212> DNA
<213> Homo sapiens

<400> 221
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<210> 222
<211> 469
<212> DNA
<213> Homo sapiens

<400> 222
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<210> 223
<211> 831
<212> DNA
<213> Homo sapiens

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<210> 224
<211> 401
<212> DNA
<213> Homo sapiens

<400> 224
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<210> 225
<211> 735
<212> DNA
<213> Homo sapiens

<400> 225
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<210> 226
<211> 862
<212> DNA
<213> Homo sapiens

<400> 226
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<210> 227
<211> 460
<212> DNA
<213> Homo sapiens

<400> 227
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<210> 228
<211> 892
<212> DNA
<213> Homo sapiens

<400> 228
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<210> 229
<211> 421
<212> DNA
<213> Homo sapiens

<400> 229
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g 421

<210> 230
<211> 605
<212> DNA
<213> Homo sapiens

<400> 230
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<210> 231
<211> 649
<212> DNA
<213> Homo sapiens

<400> 231
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<210> 232
<211> 339
<212> DNA
<213> Homo sapiens

<400> 232
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<210> 233
<211> 665
<212> DNA
<213> Homo sapiens

<400> 233
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aagtc 665

<210> 234
<211> 355
<212> DNA
<213> Homo sapiens

<400> 234
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<210> 235
<211> 672
<212> DNA
<213> Homo sapiens

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<211> 769
<212> DNA
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<400> 236
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<210> 237
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<212> DNA
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<400> 237
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<211> 525
<212> DNA
<213> Homo sapiens

<400> 238
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<210> 239
<211> 512
<212> DNA
<213> Homo sapiens

<400> 239
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<210> 240
<211> 500
<212> DNA
<213> Homo sapiens

<400> 240
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<210> 241
<211> 815
<212> DNA
<213> Homo sapiens

<400> 241
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<210> 242
<211> 881
<212> DNA
<213> Homo sapiens

<400> 242
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<211> 912

<212> DNA
<213> Homo sapiens

<400> 243
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<211> 564
<212> DNA
<213> Homo sapiens

<400> 244
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<210> 245
<211> 781
<212> DNA
<213> Homo sapiens

<400> 245
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<210> 246
<211> 557
<212> DNA
<213> Homo sapiens

<400> 246
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agtctgagtg ggcggct 557

<210> 247
<211> 526
<212> DNA
<213> Homo sapiens

<400> 247
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gccgcggggg cgtggacaca gccgcagctc cggccggtgg agctccccca gcgcacgcgc 480
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<210> 248
<211> 465
<212> DNA
<213> Homo sapiens

<400> 248
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gccagagcac gctggacccc ggagccggcg aggcccgggc gggcg 465

<210> 249
<211> 577
<212> DNA
<213> Homo sapiens

<400> 249
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<210> 250
<211> 560
<212> DNA
<213> Homo sapiens

<400> 250
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<210> 251
<211> 336
<212> DNA
<213> Homo sapiens

<400> 251
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catgtactaa taaaagaaag tctttgagta gtcaag 336

<210> 252
<211> 678
<212> DNA
<213> Homo sapiens

<400> 252
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agcagctcgg cagtgccc 678

<210> 253
<211> 783
<212> DNA
<213> Homo sapiens

<400> 253
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tac 783

<210> 254
<211> 489
<212> DNA
<213> Homo sapiens

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cgcccccttgg gcccgggccc tgccgctccc cgcctgctca agcgcgagcc cgactggggc 420
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<210> 255
<211> 586
<212> DNA
<213> Homo sapiens

<400> 255
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<210> 256
<211> 503
<212> DNA
<213> Homo sapiens

<400> 256
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<210> 257
<211> 667
<212> DNA
<213> Homo sapiens

<400> 257
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<210> 258
<211> 551
<212> DNA
<213> Homo sapiens

<400> 258
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<210> 259
<211> 791
<212> DNA
<213> Homo sapiens

<400> 259
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<210> 260
<211> 431
<212> DNA
<213> Homo sapiens

<400> 260
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<210> 261
<211> 467
<212> DNA
<213> Homo sapiens

<400> 261
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<210> 262
<211> 250
<212> DNA
<213> Homo sapiens

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<210> 263
<211> 508
<212> DNA
<213> Homo sapiens

<400> 263
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<211> 489
<212> DNA
<213> Homo sapiens

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<211> 684
<212> DNA
<213> Homo sapiens

<400> 265
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catttcatta aagatgaaaa cttt 684

<210> 266
<211> 548
<212> DNA
<213> Homo sapiens

<400> 266
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cggcggca 548

<210> 267
<211> 736
<212> DNA
<213> Homo sapiens

<400> 267
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aaacaaacaa acaaac 736

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<211> 418
<212> DNA
<213> Homo sapiens

<400> 268
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<210> 269
<211> 409
<212> DNA
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<400> 269
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<211> 598
<212> DNA
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<210> 271
<211> 430
<212> DNA
<213> Homo sapiens

<400> 271
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<210> 272
<211> 456
<212> DNA
<213> Homo sapiens

<400> 272
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<210> 273
<211> 500
<212> DNA
<213> Homo sapiens

<400> 273
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<210> 274
<211> 762
<212> DNA
<213> Homo sapiens

<400> 274
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gttgcataat caatagttat ctccttttct gagcatgaaa gc 762

<210> 275
<211> 724
<212> DNA
<213> Homo sapiens

<400> 275
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agcc 724

<210> 276
<211> 509
<212> DNA
<213> Homo sapiens
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cggctgctac ctcttcacct gcacggcgc 509

<210> 277
<211> 786

<212> DNA
<213> Homo sapiens

<400> 277
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<210> 278
<211> 512
<212> DNA
<213> Homo sapiens

<400> 278
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<210> 279
<211> 773
<212> DNA
<213> Homo sapiens

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<210> 280
<211> 805
<212> DNA
<213> Homo sapiens

<400> 280
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<210> 281
<211> 872
<212> DNA
<213> Homo sapiens

<400> 281
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<210> 282
<211> 486
<212> DNA
<213> Homo sapiens

<400> 282
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gccttc 486

<210> 283
<211> 515
<212> DNA
<213> Homo sapiens

<400> 283
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<210> 284
<211> 629
<212> DNA
<213> Homo sapiens

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<210> 285
<211> 409
<212> DNA
<213> Homo sapiens

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<210> 286
<211> 380
<212> DNA
<213> Homo sapiens

<400> 286
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<210> 287
<211> 690
<212> DNA
<213> Homo sapiens

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atgggcattt ttaaatgtta cggcatatgc taatataata ttatggcatt aaataaaaac 660
aagaagagaa ctgactaaaa ccaaaaaacc 690

<210> 288
<211> 400
<212> DNA
<213> Homo sapiens

<400> 288
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<210> 289
<211> 490
<212> DNA
<213> Homo sapiens

<400> 289
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<210> 290
<211> 497
<212> DNA
<213> Homo sapiens

<400> 290
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tcaatatccc tgcagtg 497

<210> 291
<211> 713
<212> DNA
<213> Homo sapiens

<400> 291
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<210> 292
<211> 510
<212> DNA
<213> Homo sapiens

<400> 292
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<210> 293
<211> 559
<212> DNA
<213> Homo sapiens

<400> 293
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taaataaaca aaaagtgcc 559

<210> 294
<211> 444
<212> DNA
<213> Homo sapiens

<400> 294
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gatgtctcca tggtgacctc cttgggggtc actgaccctg cttggtgggg tccccttgt 420
aacaataaaa tctatttaaa cttg 444

<210> 295
<211> 889
<212> DNA
<213> Homo sapiens

<400> 295
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<210> 296
<211> 687
<212> DNA
<213> Homo sapiens

<400> 296
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<210> 297
<211> 596
<212> DNA
<213> Homo sapiens

<400> 297
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<210> 298
<211> 694
<212> DNA
<213> Homo sapiens

<400> 298
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tgaggaaaaa aataaaactc aaaaagcttt gtgg 694

<210> 299
<211> 539
<212> DNA
<213> Homo sapiens

<400> 299
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<210> 300
<211> 561
<212> DNA
<213> Homo sapiens

<400> 300
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<210> 301
<211> 804
<212> DNA
<213> Homo sapiens

<400> 301
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<211> 659
<212> DNA
<213> Homo sapiens

<400> 302
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<210> 303
<211> 883
<212> DNA
<213> Homo sapiens

<400> 303
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<210> 304
<211> 597
<212> DNA
<213> Homo sapiens

<400> 304
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<213> Homo sapiens

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<211> 748
<212> DNA
<213> Homo sapiens

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<211> 909
<212> DNA
<213> Homo sapiens

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<211> 603
<212> DNA
<213> Homo sapiens

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<211> 314
<212> DNA
<213> Homo sapiens

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<210> 310
<211> 677
<212> DNA
<213> Homo sapiens

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<210> 311
<211> 766
<212> DNA
<213> Homo sapiens

<400> 311
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<211> 550
<212> DNA
<213> Homo sapiens

<400> 312
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<210> 313
<211> 868
<212> DNA
<213> Homo sapiens
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<211> 592
<212> DNA
<213> Homo sapiens

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<211> 405
<212> DNA
<213> Homo sapiens

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<210> 316
<211> 771
<212> DNA
<213> Homo sapiens

<400> 316
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<210> 317
<211> 664
<212> DNA
<213> Homo sapiens

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ctcc 664

<210> 318
<211> 706
<212> DNA
<213> Homo sapiens

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<210> 319
<211> 493
<212> DNA
<213> Homo sapiens

<400> 319
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<210> 320
<211> 514
<212> DNA
<213> Homo sapiens

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<211> 395
<212> DNA
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<210> 322
<211> 550
<212> DNA
<213> Homo sapiens

<400> 322
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<210> 323
<211> 415
<212> DNA
<213> Homo sapiens

<400> 323
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<210> 324
<211> 763

<212> DNA
<213> Homo sapiens

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<211> 1955
<212> DNA
<213> Homo sapiens

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<211> 506
<212> DNA

<213> Homo sapiens

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<210> 342
<211> 1755

<212> DNA
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<213> Homo sapiens

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<213> Homo sapiens

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<211> 1974
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<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<211> 1684
<212> DNA
<213> Homo sapiens

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<211> 1514
<212> DNA
<213> Homo sapiens

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<211> 279
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<213> Homo sapiens

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<211> 2001
<212> DNA
<213> Homo sapiens
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<212> DNA
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<213> Homo sapiens

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<211> 1933
<212> DNA
<213> Homo sapiens

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<211> 1862
<212> DNA
<213> Homo sapiens

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<211> 1690
<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<211> 1661
<212> DNA
<213> Homo sapiens

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<211> 1851
<212> DNA
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<212> DNA
<213> Homo sapiens

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<211> 799
<212> DNA

<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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<212> DNA
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<213> Homo sapiens

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<213> Homo sapiens

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<211> 2262
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<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<211> 1875
<212> DNA
<213> Homo sapiens

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<212> DNA
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<211> 2061
<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/77290 A3

(54) Title: POLYNUCLEOTIDES ENCODING NOVEL SECRETED PROTEINS

(57) Abstract: Isolated polynucleotides which have been derived from a variety of human tissue sources, and which encode novel secreted proteins, are provided. Also provided are methods for producing proteins using these polynucleotides, and the proteins so produced.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/10295

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 23.5, 24.31; 530/300, 350; 435/6, 69.1, 252.3, 320.1, 325

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database: GenEmbl; Accession NO: AC002401; Birren et al. "Homo sapiens chromosome 17, clone RPC875H18", complete sequence; 10 November 1997; having 98.5% sequence identity to SEQ ID NO: 1, see entire document.	1-4
X, P	Database: EST; Accession NO: AL525190; Li et al.: "Full length cDNA libraries and normalization"; 13 February 2001; having 81.1% sequence identity to SEQ ID NO: 1; vector: pCMVSPORT 6; host cell: DH10B; see entire document.	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 NOVEMBER 2001	31 DEC 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Janice Bridges for RITA MITRA Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/10295

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-7, all in part (SEQ ID NO. 1.

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/10295

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

C07H 21/02, 21/04; C07K 5/00, 14/00; C12Q 1/68, C12P 21/06, C12N 1/20, 15/63, 5/00

A. CLASSIFICATION OF SUBJECT MATTER.
US CL :

536/23.1, 23.5, 24.31; 530/300, 350; 435/6, 69.1, 252.3, 320.1, 325

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used)

Sequence Search (Database: GenEmbl, N_Geneseq_0601, EAST, Issued_Patents_NA)

EAST (Database: USPAT, DERWENT, EPO, JPO)

STN (Database: BIOSIS, CAPLUS, EMBASE, MEDLINE, SCISEARCH)

Search Terms: polynucleotide, DNA, nucleic acid, secreted protein

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1 In order for all inventions to be searched, the appropriate additional search fees must be paid.

Groups 1-625, claims 1-7, all in part, drawn to the special technical feature of an isolated nucleic acid of SEQ ID NO 1-625, vector, host cell and process for producing protein, wherein values of SEQ IDs 1-625 of claim 1 correspond to values of SEQ ID NO: 1-625 of claims 2 and 3. For examples.

Group 1 is the main invention and this correlates to SEQ ID NO 1 of claims 1-3
If group 2 is elected, this correlates to SEQ ID NO. 2 of claims 1-3

Groups 626-1250, claim 8, in part, drawn to the special technical feature of a protein encoded by the polynucleotides of SEQ ID NO: 1-625, wherein values of SEQ IDs 1-625 of claim 8 correspond to values of SEQ ID NO 1-625 of claims 1-3. For examples.

If group 626 is elected, this correlates to SEQ ID NO 1 of claims 1-3
If group 627 is elected, this correlates to SEQ ID NO. 2 of claims 1-3.

Groups 1251-1875, claim 9, in part, drawn to the special technical feature of an isolated antibody which binds to a protein encoded by the polynucleotides of SEQ ID NO 1-625, wherein values of SEQ IDs 1-625 of claim 9 correspond to values of SEQ ID NO: 1-625 of claims 1, 2 and 3. For examples.

If group 1251 is elected, this correlates to SEQ ID NO 1 of claims 1-3
If group 1252 is elected, this correlates to SEQ ID NO 2 of claims 1-3

Groups 1876-2500, claims 10, 12, 13, all in part, drawn to the special technical feature of a method of detecting a protein in a biological sample by determining the binding of the protein by a specific antibody, wherein the protein is encoded by the polynucleotides of SEQ ID NO 1-625, wherein values of SEQ IDs 1-625 of claims 10, 12, 13 correspond to values of SEQ ID NO 1-625 of claims 1, 2 and 3. For examples.

If group 1876 is elected, this correlates to SEQ ID NO 1 of claims 1-3
If group 1877 is elected, this correlates to SEQ ID NO 2 of claims 1-3

Groups 2501-3125, claims 11, 14, 15, all in part, drawn to the special technical feature of a method of detecting a polynucleotide in a biological sample by determining the hybridization of the polynucleotide by a polynucleotide reagent, wherein the polynucleotide is set forth in SEQ ID NO. 1-625, wherein values of SEQ IDs 1-625 of claims 11, 12, 13 correspond to values of SEQ ID NO. 1-625 of claims 1, 2 and 3. For examples.

If group 2501 is elected, this correlates to SEQ ID NO 1 of claims 1-3

If group 2502 is elected, this correlates to SEQ ID NO: 2 of claims 1-3

Groups 3126-3750, claim 16, in part, drawn to the special technical feature of a method of identifying a compound that modulates the activity of the protein by monitoring the effect of the test compound on the activity of the protein, wherein the protein is encoded by the polynucleotides of SEQ ID NO: 1-625, wherein values of SEQ IDs 1-625 of claim 14 correspond to values of SEQ ID NO: 1-625 of claims 1, 2 and 3. For examples,

If group 3126 is elected, this correlates to SEQ ID NO: 1 of claims 1-3.
If group 3127 is elected, this correlates to SEQ ID NO: 2 of claims 1-3.

Groups 3751-4375, claim 17, in part, drawn to the special technical feature of a method of identifying a compound that modulates the expression of the polynucleotide by monitoring the effect of the test compound on the expression of the polynucleotide, wherein polynucleotide is set forth in SEQ ID NO: 1-625, wherein values of SEQ IDs 1-625 of claim 15 correspond to values of SEQ ID NO: 1-625 of claims 1, 2 and 3. For examples,

If group 3751 is elected, this correlates to SEQ ID NO: 1 of claims 1-3.
If group 3752 is elected, this correlates to SEQ ID NO: 2 of claims 1-3

Groups 4376-5000, claim 18, in part, drawn to the special technical feature of a method of identifying a compound that modulates the production of the protein by monitoring the effect of the test compound on the production of the protein, wherein the protein is encoded by the polynucleotides of SEQ ID NO: 1-625, wherein values of SEQ IDs 1-625 of claim 16 correspond to values of SEQ ID NO: 1-625 of claims 1, 2 and 3. For examples,

If group 4376 is elected, this correlates to SEQ ID NO: 1 of claims 1-3.
If group 4377 is elected, this correlates to SEQ ID NO: 2 of claims 1-3.

Groups 5001-5625, claim 19, in part, drawn to the special technical feature of a method for treating a disorder characterized by aberrant expression of the polynucleotide by administering a compound that modulates expression of the polypeptide, wherein polynucleotide is set forth in SEQ ID NO: 1-625, wherein values of SEQ IDs 1-625 of claim 17 correspond to values of SEQ ID NO: 1-625 of claims 1, 2 and 3. For examples,

If group 5001 is elected, this correlates to SEQ ID NO: 1 of claims 1-3
If group 5002 is elected, this correlates to SEQ ID NO: 2 of claims 1-3

Groups 5626-6250, claim 20, in part, drawn to the special technical feature of a method for treating a disorder characterized by aberrant production of the protein by administering a compound that modulates production of the protein, wherein the protein is encoded by the polynucleotides set forth in SEQ ID NO: 1-625, wherein values of SEQ IDs 1-625 of claim 18 correspond to values of SEQ ID NO: 1-625 of claims 1, 2 and 3. For examples,

If group 5626 is elected, this correlates to SEQ ID NO: 1 of claims 1-3
If group 5627 is elected, this correlates to SEQ ID NO: 2 of claims 1-3

Groups 6251-6875, claim 21, in part, drawn to the special technical feature of a method for treating a disorder characterized by aberrant activity of the protein by administering a compound that modulates activity of the protein, wherein,the protein is encoded by the polynucleotides set forth in SEQ ID NO: 1-625, wherein values of SEQ IDs 1-625 of claim 19 correspond to values of SEQ ID NO: 1-625 of claims 1, 2 and 3. For examples,

If group 6251 is elected, this correlates to SEQ ID NO: 1 of claims 1-3
If group 6252 is elected, this correlates to SEQ ID NO: 2 of claims 1-3

The inventions listed as Groups 1-6875 do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking groups 1-6875 appears to be that they all relate to a polynucleotide. However it is apparent that SIGMA Catalog, 1999, page 1610 discloses a primer with poly T, wherein said primer renders claim 3 among others not novel (for example see SEQ ID NO: 314, poly A, and SEQ ID NO: 176, poly T), because poly T primer is capable to hybridize to SEQ ID NO: 314 and to a complement of SEQ ID NO: 176. This technical feature does not constitute a special technical feature as it does not define a contribution over the prior art.

The nucleic acids and proteins of each of the invention do not share the same or corresponding special technical feature with each other. The special technical feature of each DNA molecule is considered to be the structure as determined by its SEQ ID NOs: 1-625.

The special technical feature of each protein molecule is considered to be the structure as determined by its amino acid sequence encoded by the polynucleotides of SEQ ID NOs: 1-625.

INTERNATIONAL SEARCH REPORT

International application No.
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The antibody specific to the proteins of the invention has a special technical feature with respect to its structure and physicochemical properties.

Additionally the claimed methods do not share the same technical feature as set forth above and they lack unity of invention because methods are alternate methods of use.

Accordingly, Groups 1-6875 are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept and so lack unity of invention.